IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ruggero FARIELLO *et al.*	Docket No:	373987–011 US (102895)
Serial No.:	10/559,982	Confirmation No.:	6583
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For:	METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE	Examiner:	Sahar JAVANMARD

DECLARATION OF C. WARREN OLANOW UNDER 37 C.F.R. § 1.132

I, **C. WARREN OLANOW,** M.D., FRCPC, declare and state as follows:

A. Background and Credentials

1. I am the Henry P. and Georgette Goldschmidt Professor of Neurology in the Department of Neurology and Professor in the Department of Neuroscience at the Mount Sinai School of Medicine (Mount Sinai), New York, NY. I was Chairman of the Department of Neurology and Chief of the Neurology service at Mount Sinai between 1994 and 2009. I am also Director of the Robert and John M. Bendheim Parkinson's Disease Center at the Mount Sinai Medical Center.

2. I have been President of the Movement Disorder Society, President of the International Society of Motor Disturbances, and Treasurer of the American Neurological Society.

3. I have devoted nearly the entirety of my career to the study of the cause and treatment of Parkinson's disease.

4. I have studied and performed clinical trials on many of the drugs that are now commonly used to treat Parkinson's disease, including:

- Sinemet: a combination of levodopa and the peripheral decarboxylase inhibitor, carbidopa (aka MK-486), *see* Olanow *et al.*, "Double-blind controlled study of MK-486," *Transactions of the Amer. Neurol. Ass'n* 98:301-303 (1973) (Exhibit 1); Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, Olanow CW, Tanner C, Marek K, Parkinson Study Group, "Does levodopa slow or hasten the rate of progression of Parkinson disease? The results of the Elldopa study," *N Eng J Med* 351: 2498-2508 (2004) (Exhibit 2);

- Sinemet CR: a controlled release combination of levodopa and carbidopa, *see* Olanow *et al.*, "An open multi-center trial of Sinemet CR in levodopa naïve Parkinson's disease patients," *Clin. Neuropharm.* 14:235-240 (1991) (Exhibit 3);

- Pergolide (Permax): a dopamine agonist, that is now withdrawn from the U.S. market), *see* Olanow *et al.*, "A double-blind controlled study of pergolide mesylate as an adjunct to Sinemet in the treatment of Parkinson's disease," *Adv. in Neurol.* 45:555-560 (1987) (Exhibit 4) and Olanow *et al.*, "A double-blind controlled study of pergolide mesylate in the treatment of Parkinson's disease," *Clinical Neuropharm.* 10:178-185 (1987) (Exhibit 5); and Olanow *et al.*, "A multi-center, double-blind, placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease," *Movement Disorders* 9: 40-47 (1994);

- Deprenyl (Selegiline): a selective monoamine oxidase (MAO) B inhibitor, , *see* Parkinson Study Group (C.W. Olanow, Steering Committee), "Effect of Deprenyl on the progression of disability in early Parkinson's disease," *N. Engl. J. Med.* 321:1364-1371 (1989) (Exhibit 6); and Olanow CW *et al.*, "The effect of deprenyl and levodopa on the progression of signs and symptoms in Parkinson's disease," *Ann Neurol* 38: 771-777 (1995);

- Pramipexole (Mirapex): a dopamine agonist, *see* Parkinson Study Group (C.W. Olanow, Steering Committee), "Safety and efficacy of pramipexole in early Parkinson's disease: a randomized dose-ranging study," *JAMA* 278:125-130 (1997) (Exhibit 7);

- Ropinirole (Requip): a dopamine agonist, *see* Lieberman *et al.*, "A multi-center double blind placebo-controlled trial of ropinirole as an adjunct to L-dopa in the treatment of Parkinson's disease patients with motor fluctuations," *Neurology* 51:1057-1062 (1998) (Exhibit 8);

- Tolcapone (Tasmar): a catechol O-methyl transferase (COMT) inhibitor, *see* Olanow CW (for the Tasmar advisory board), "Tolcapone (Tasmar) and hepatotoxic effects," *Arch. Neurol.* 57:263-267 (2000) (Exhibit 9); and Olanow

CW, Watkins PB, "Tolcapone 2007: An Efficacy and Safety Review," *J Clin Neuropharm* 30:287-294 (2007) (Exhibit 10);

- Entacapone (Comtan, and in combination with levodopa, Stalevo): a COMT inhibitor, , *see* Olanow *et al.*, "Controlled study of entacapone in levodopa-treated stable Parkinson's disease patients," *Arch. Neurol.* 61:1563-1568 (2004) (Exhibit 11);

- Rasagiline (Azilect): an irreversible MAO inhibitor *see* Stern *et al.*, "A double-blind, randomized controlled trial of rasagiline as monotherapy in early Parkinson's disease patients," *Movement Disorders* 19:916-923 (2004) (Exhibit 12); Olanow *et al.*, "A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson's disease (the ADAGIO study): rationale, design, and baseline characteristics," *Movement Disorders* 23:2194-2201 (2008) (Exhibit 13); and

- Lisuride: a dopamine agonist (not approved in the United States), *see* Stocchi *et al.*, "Prospective randomized trial of lisuride infusion versus oral levodopa in PD patients," *Brain* 125:2058-2066 (2002) (Exhibit 14).

5. I have also been an investigator in clinical trials of drugs that remain promising, but have yet to reach the clinic, and others that have failed clinical trials in Parkinson's patients, including:

- CV 205-502 (CV): a long-acting dopamine agonist with potent D2 and weak D1 activity, *see* Olanow *et al.*, "CV205-502: Safety, toleration and efficacy of increasing dose in patients with Parkinson's disease, with double-blind placebo crossover," *Clinical Neuropharm.* 12:490-497 (1989) (Exhibit 15);

- TCH346: a putative neuroprotective drug with anti-apoptotic effects, *see* Olanow *et al.*, "TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial," *Lancet Neurol.* 5:1013-1020 (2006) (Exhibit 16);

- Sarizotan (EMD 128130): a chromane derivative that exhibits affinity at serotonin and dopamine receptors, *see* Olanow *et al.*, "Multicenter, open-label, trial of Sarizotan in Parkinson's disease patients with levodopa-induced dyskinesias (the SPLENDID study)," *Clin. Neuropharm.* 27:58-62 (2004) (Exhibit 17); and Goetz *et al.*, "Sarizotan as a treatment for dyskinesias in Parkinson's disease: a double-blind placebo-controlled trial," *Movement Disorders* 22:179-186 (2007) (Exhibit 18);

- Lazabemide: a selective, reversible, MAO-B inhibitor, *see* Parkinson Study Group (Olanow CW, Steering Committee), "A controlled clinical trial of lazabemide (Ro 19-6327) in untreated Parkinson's disease," *Ann. Neurol.* 33:350-356 (1993)

(Exhibit 19); Parkinson Study Group (Olanow CW, Steering Committee), "A controlled trial of lazabemide (Ro 19-6327) in levodopa treated Parkinson's disease," *Arch. Neurol.* 51:342-347 (1994) (Exhibit 20); Parkinson Study Group (Olanow CW, Steering Committee), "Effect of lazabemide on the progression of disability in early Parkinson's disease," *Ann. Neurol.* 40:99-107 (Exhibit 21).

6. Over the years, I have also participated in, and at times designed and run, clinical trials of potential non-pharmacological therapies for Parkinson's disease, including:

(i) Deep Brain Stimulation

- The Deep Brain Stimulation for PD Study Group (Obeso and Olanow, corresponding authors), "Deep brain stimulation of the subthalamic nucleus or globus pallidus pars interna in Parkinson's disease," *New Engl. J. Med.* 345:956-963 (2001) (Exhibit 22);
- Morrison *et al.*, "A program for neuropsychological investigation of deep brain stimulation (PNIDBS) in movement disorder patients: development, feasibility, and preliminary data," *Neuropsychiatry, Neuropsychol. Behav. Neurol.* 13:204-219 (Exhibit 23);
- Koller *et al.*, "High frequency unilateral thalamic stimulation in the treatment of essential and Parkinsonian tremor," *Ann. Neurol.* 42:292-299 (1997) (Exhibit 24);
- Olanow *et al.*, "The role of deep brain stimulation as a surgical treatment for Parkinson's disease," *Neurology* 55 (suppl. 6):60-66 (2000) (Exhibit 25);
- Germano *et al.*, "Unilateral stimulation of the subthalamic nucleus in Parkinson's disease – a double blind 12-month study," *J. Neurosurgery* 101:36-42 (2004) (Exhibit 26);

(ii) fetal nigral cell transplantation

- Olanow *et al.*, "Clinical pattern and risk factors for dyskinesias following fetal nigral transplantation in Parkinson's disease: a double-blind video-based analysis," *Movement Disorders* 24:336-343 (2009) (Exhibit 27);
- Kordower *et al.*, "Transplanted dopaminergic neurons develop PD pathologic changes: a second case report," *Movement Disorders* 23:2303-2306 (2008) (Exhibit 28);
- Kordower *et al.*, "Parkinson's disease pathology in long-term embryonic nigral transplants in Parkinson's disease," *Nature Med.* 14:504-506 (2008) (Exhibit 29);

- Olanow *et al.*, "A double-blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease," *Ann Neurol.* 54(3):403-14 (2003) (Exhibit 30);

- Hauser *et al.*, "Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease," *Arch Neurol.* 56(2):179-87 (1999) (Exhibit 31);

- Freeman *et al.*, "Use of placebo surgery in a controlled trial of a cellular-based therapy for Parkinson's disease," *N. Engl. J. Med.* 341:988-992 (1999) (Exhibit 32);

- Kordower *et al.*, "Fetal nigral grafts survive and mediate clinical benefit in a patient with Parkinson's disease," *Movement Disorders* 13(3):383-93 (1998) (Exhibit 33);

- Kordower *et al.*, "Fetal grafting for Parkinson's disease: expression of immune markers in two patients with functional fetal nigral implants," *Cell Transp.* 6: 213-219 (1997) (Exhibit 34);

- Kordower *et al.*, "Dopaminergic transplants in patients with Parkinson's disease: neuroanatomical correlates of clinical recovery," *Exp. Neurology* 144:41-46 (1997) (Exhibit 35);

- Olanow *et al.*, "Fetal nigral transplantation as a therapy for Parkinson's disease," *Trends. Neurosci.* 19:102-109 (1996) (Exhibit 36);

- Kordower *et al.*, "Functional fetal nigral grafts in a patient with Parkinson's disease: chemoanatomic, quantitative, ultrastructural, and metabolic studies," *J. Comp. Neurol.* 370:203-230 (1996) (Exhibit 37);

- Kordower *et al.*, "Neuropathologic evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease," *N. Engl. J. Med.* 332:1118-1124 (1995) (Exhibit 38);

- Freeman *et al.*, "Bilateral fetal nigral transplantation into the postcommissural putamen in Parkinson's Disease," *Ann. Neurol.* 38:379-388 (1995) (Exhibit 39); and

(iii) gene therapy

- Marks *et al.*, "Gene transfer of a trophic factor for Parkinson's disease: initial clinical trial with AAV2-neurturin (CERE-120)," *Lancet Neurol.* 7:400-408 (2008) (Exhibit 40).

7. I have also participated over the years in efforts to define improved clinimetric measures necessary to improve the sensitivity and/or the predictive power of rating scales used in clinical trials in Parkinson's disease. *See, e.g.*,

- Goetz *et al.* for the Movement Disorder society UPDRS Revision Task Force, "Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results," *Movement Disorders* 23:2129-2170 (2008) (Exhibit 41);
- Martinez-Martin *et al.*, "Prevalence of nonmotor symptoms in Parkinson's disease in an international setting: study using nonmotor symptoms questionnaire in 545 patients," *Movement Disorders* 22:1623-1629 (2007) (Exhibit 42);
- Emre *et al.*, "Clinical diagnostic criteria for dementia associated with Parkinson's disease," *Movement Disorders* 22:1689-1707 (2007) (Exhibit 43);
- Dubois *et al.*, "Movement Disorder Society Task Force: Diagnostic Procedures for Parkinson's disease dementia," *Movement Disorders* 222:2314-2324 (2007) (Exhibit 44);
- Chauduri *et al.*, "The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study," *Movement Disorders* 22:1901-1911 (2007) (Exhibit 45);
- Goetz *et al.*, "Movement disorder society-sponsored revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS): Process, format and clinimetric testing plan," *Movement Disorders* 22:41-47 (2007) (Exhibit 46);
- Chaudhuri *et al.*, "International multicentre pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study," *Movement Disorders* 21:916-923 (2006) (Exhibit 47);
- Cho *et al.*, "A model-based approach for assessing Parkinsonian gait and effects of levodopa and deep-brain stimulation," *IEEE J. Quantum Electronics* 1:1228-1231 (2006) (Exhibit 48).

8. My research efforts have not been limited, however, to the conduct of clinical trials, the last of the hurdles to be surmounted in bringing new therapies into clinical practice. Parkinson's disease is a progressive neurodegenerative disorder of unknown etiology; lacking known cause, we term the disease "idiopathic". In the laboratory, we continue to seek potential environmental and genetic factors that might contribute to the genesis of idiopathic Parkinson's disease, to translate these preclinical insights into improved animal models, and through the use of such models, to translate this understanding into improved human therapies.

9. For example, we have explored whether perturbation of the ubiquitin-proteasome system might be a contributing factor in the development of Parkinson's disease. *See, e.g.*,

- McNaught *et al.*, "Proteasomal dysfunction in Parkinson's disease," *Neurology* 66(10 Suppl 4):S37-49 (2006) (Exhibit 49);
- Nair *et al.*, "P53 mediates non-transcriptional cell death in dopaminergic cells in response to proteasome inhibitors," J. Biol. Chem. 281:39550-39560 (2006) (Exhibit 50);
- Mytilineou *et al.*, "Inhibition of Proteasome Activity Sensitizes Dopamine Neurons to Heat Shock Treatment and Oxidative Stress," *J. Neural Transmission* 111:1237-1251 (2004) (Exhibit 51);
- McNaught *et al.*, "Impairment of the ubiquitin-proteasome system causes dopaminergic cell death and inclusion body formation in ventral mesencephalic cultures," *J. Neurochem* 81: 301-306 (2002) (Exhibit 52);
- McNaught *et al.*, "Proteasomal inhibition causes nigral degeneration with inclusion bodies in rats," *NeuroReport* 13:1437-1441 (2002) (Exhibit 53);
- McNaught *et al.*, "Failure of the ubiquitin-proteasome system in Parkinson's disease," *Nature Reviews Neuroscience* 2: 589-594 (2001) (Exhibit 54).

As I discuss at greater length later in this Declaration, current animal models do a poor job of modeling the behavioral changes, progressive course and full spectrum of pathology that occur in idiopathic Parkinson's disease, and are poor at predicting ultimate efficacy in human clinical trials. As a consequence, we have applied our *in vitro* work on proteasomal disruption to attempt to create a new animal model of progressive disease:

- McNaught K and Olanow CW, "The proteasome inhibition model of Parkinson's disease," *Ann Neurol.* 60:243-247 (2006) (Exhibit 55);
- McNaught *et al.*, "Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson's disease," *Ann. Neurol.* 56:149-162 (2004) (Exhibit 56).

10. We have also studied oxidative stress and various metals in Parkinson disease patients, and attempted to generate models of Parkinsonism using oxidative stress and various metals:

- Sengstock *et al.*, "Intranigral iron infusion in the rat. Acute elevations in nigral lipid peroxidation and striatal dopaminergic markers with ensuing nigral degeneration," *Biol. Trace Elem. Res.* 58:177-195 (1997) (Exhibit 57);

- Jenner *et al.*, "Oxidative stress and the pathogenesis of Parkinson's disease," *Neurology* 47 (suppl 3):161-170 (1996) (Exhibit 58);
- Hauser *et al.*, "Blood manganese correlates with brain magnetic resonance imaging changes in patients with liver disease," *Can. J. Neurol. Sci.* 23:95-98 (1996) (Exhibit 59);
- Oestreicher *et al.*, "Degeneration of nigrostriatal dopaminergic neurons increases iron within the substantia nigra: a histochemical and neurochemical study," *Brain Res.* 660: 8-18 (1994) (Exhibit 60);
- Olanow, "The role of iron and oxidant stress in Parkinson's disease and aging," *Ann. Neurol.* 32:2-9 (1992) (Exhibit 61);
- Good *et al.*, "Neuromelanin-containing neurons of the substantia nigra accumulate iron and aluminum in Parkinson's disease: A LAMMA study," *Brain Res.* 593:343-346 (1992) (Exhibit 62);
- Sengstock *et al.*, "Infusion of iron into the rat substantia nigra: nigral pathology and dose-dependent loss of striatal dopaminergic markers," *J. Neurosci. Res.* 35:67-82 (1993) (Exhibit 63);
- Huang *et al.*, "Progression after chronic manganese exposure," *Neurology* 43:1479-1483 (1993) (Exhibit 64);
- Olanow *et al.*, "Free Radicals and Neurodegeneration," *Trends Neurosci.*17: 193-194 (1994) (Exhibit 65);
- Calne *et al.*, "Manganism and Idiopathic Parkinsonism, Similarities and Differences," *Neurology* 44:1583-1586 (1994) (Exhibit 66);
- Shinotoh *et al.*, "MRI and PET studies of manganese-intoxicated monkeys," *Neurology* 45:1199-1204 (1995) (Exhibit 67);
- Sengstock *et al.*, "Progressive changes in striatal dopaminergic markers, nigral volume, and rotational behavior following iron infusion into the rat substantia nigra," *Exp. Neurol.* 130:82-94 (1994) (Exhibit 68).

11. I have been elected by my peers to a variety of leadership positions in international organizations devoted to Parkinson's and related diseases, including:

1990 – 1992: Vice President, International Society of Motor Disturbances

1992 – 1994: President, International Society of Motor Disturbances

1992 – 1995: Treasurer, Movement Disorder Society

2001 : President, International World Conference on Neurodegeneration

2002-2006 : Treasurer, American Neurological Association

2003 – 2004: President, Movement Disorders Society

In addition, I have been appointed an honorary professor at the Royal Free Hospital of the University College London and an honorary member of the French Neurological Society. I have delivered plenary and keynote lectures at multiple international society meetings related to Parkinson's Disease, and I have been visiting professor at universities throughout the world. In 2007, I received the Presidential Award from the Movement Disorder Society. I was also ranked #1 in the United States and #4 in the world for the number of citations for articles related to Parkinson's Disease during the years 1996 – 2006. My *Curriculum Vitae* is enclosed herewith as Exhibit 69.

B. Terms of Engagement

12. I understand that U.S. patent application serial no. 10/559,982 (the "present" or "instant" application) is owned by Newron Pharmaceuticals, S.p.A.("Newron") and is exclusively licensed to Merck Serono, S.A ("Merck Serono"). It has been announced publicly that Merck Serono is leading the clinical development of Safinamide for use in Parkinson's disease.

13. I have been engaged as a consultant to Newron, and my work on this Declaration falls within the scope of those consulting activities. According to the terms of that engagement, I am compensated at my usual hourly consulting rate. I have never held equity in Newron, currently hold no equity in Newron, and my consulting agreement does not provide any options to acquire equity in Newron. I receive no other compensation directly or indirectly from Newron, and my laboratory does not receive and has not received any funding from Newron or any of its affiliates.

14. I am also currently a consultant to Merck Serono and have previously served as a consultant to Merck KGaA, one of its corporate predecessors. My work on the present Declaration does not fall within the scope of my consulting arrangements with Merck Serono or

Merck KGaA. For purpose of completeness, however, I note here that Merck Serono compensates me for relevant consulting activities at my usual hourly consulting rate and that I have previously received compensation for consulting activities with Merck KGaA. I have never held equity in Merck Serono or in either of its predecessor companies, Merck KGaA and Serono S.A. I currently hold no equity in Merck Serono, and my consulting agreement does not provide any options to acquire equity in Merck Serono. I receive no other compensation directly or indirectly from Merck Serono or Merck KGaA, and to the best of my knowledge, my laboratory does not today receive any funding from any of these entities.

15. My *curriculum vitae* (attached hereto as Exhibit 69) provides a list of Industry Appointments beginning in 1988 and a separate list of public and private grant support for my laboratory from 1975 to the present day. Although I have striven for completeness, the document may contain some errors and omissions in the description of my industry relationships over the past 30 years. Accordingly, I want to emphasize here that the views I am expressing in this Declaration are entirely my own, and have not been influenced by any pecuniary interest in the outcome. Furthermore, the views expressed in this Declaration do not necessarily reflect the views of Mount Sinai School of Medicine, Mount Sinai Medical Center, or any other organization or entity for which I work, consult, or with which I am affiliated.

16. For purposes of this Declaration, I was asked by Newron to consider the following questions.

(*i*) Would the disclosure in the Fredriksson reference[1] have provided a person of ordinary skill in the art of Parkinson's disease therapy, in April 2003, with a reasonable expectation that the oral administration of safinamide (or safinamide salt), on a daily dosage schedule of about 0.5 to about 2 mg/kg/day (or on a daily dosage schedule of no more than about 150 mg/day), would increase the therapeutic efficacy of a

[1] Fredriksson *et al.*, "Effects of co-administration of anticonvulsant and putative anticonvulsive agents and sub-/suprathreshold doses of L-Dopa upon motor behaviour of MPTP-treated mice," *J. Neural. Transm.* 106:889-909 (1999) ("Fredriksson") (of record).

clinically effective dose of concurrently administered L-Dopa, administered with a peripheral decarboxylase inhibitor, in the treatment of idiopathic Parkinson's disease?

(*ii*) Would the additional disclosures in the Chazot[2] and Fariello[3] references change that assessment?

For the reasons elaborated at some length below, I would answer both questions in the negative.

C. Fredriksson

17. Fredriksson reports two experiments in which safinamide (FCE 26743) was co-administered with L-Dopa in a rodent model of Parkinson's disease, namely, MPTP-lesioned C57 BL/6 mice.

18. The MPTP model dates from the mid-1980s. Despite significant drawbacks that are more notable in rodents than in primates, the MPTP model (particularly in primates) is often used in preclinical research on Parkinson's disease drugs. I understand, for example, that Newron itself submitted data from such a model in its Investigational New Drug application (IND) to FDA. We ourselves have used MPTP-lesioned animals, albeit primates, in various studies. *See*, *e.g.*,

- Smith *et al.*, "Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naive primates," *Movement Disorders* 20:306-314 (2005) (Exhibit 71).

19. After injection into a suitable test animal, the highly lipophilic MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) crosses the blood-brain barrier, where it is oxidized by

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[2] Chazot, "Safinamide – Newron Pharmaceuticals", *Curr. Opin. Investigational Drugs* 2(6):809-813 (2001) (of record).

[3] Maj *et al.*, "PNU-151774E, a combined MAO-B and glutamate release inhibitor, is effective in animal models of Parkinson's disease," Society for Neuroscience Abstracts 25 (1-2): p 1599 (1999) (Fariello, senior author) (Exhibit 70).

monoamine oxidase to MPP^+ (1-methyl-4-phenylpyridinium). MPP^+ is then actively transported by the dopamine transporter, for which it has high affinity, into dopaminergic neurons. MPP^+ acts as an intracellular toxin, leading to death of dopaminergic cells in the substantia nigra. This selective lesion of dopaminergic neurons in the substantia nigra mimics the dopamine lesion that occurs in idiopathic Parkinson's disease, and causes bradykinesia or slowness and rigidity or stiffness. And, – like idiopathic Parkinson's disease – these symptoms are responsive to L-dopa and various dopamine agonists in MPTP monkeys.

20. Despite the apparent mimicry of certain pathologic features and symptoms of idiopathic Parkinson's disease, the MPTP model is known to fall far short of recapitulating other, critical, components of idiopathic Parkinson's disease. The hallmark pathological feature of idiopathic Parkinson's disease is an intracellular proteinaceous inclusion known as the Lewy Body; in the MPTP model, Lewy bodies are not detected. Idiopathic Parkinson's disease is a chronic, progressive, neurodegenerative disorder; by contrast, in the standard MPTP model, the lesion is made acutely, and does not then progress. Idiopathic Parkinson's disease is known to include degeneration of non-dopaminergic extra-nigral neurons in the cerebral hemisphere, brain stem, spinal cord, and peripheral autonomic nervous system; whereas, in the MPTP model, the lesion is largely restricted to the substantia nigra (and Locus Coeruleus) and such extra-nigral damage is not detected. As it progresses, idiopathic Parkinson's disease causes autonomic dysfunction, sleep disturbances, mood disorders, psychosis and dementia, none of which are prominent featers of animals that are acutely lesioned with MPTP. In particular, acute MPTP lesions in lower mammals, and even primates, is not known to reproduce the cognitive and affective impairments (such as depression) that are routinely seen as the disease progresses in human patients.

21. Despite the apparent mimicry of certain pathologic features and symptoms of idiopathic Parkinson's disease, the MPTP mouse model has been shown over the years to be a poor model for predicting efficacy of potential therapeutic agents in human patients.[4] Some

[4] The same can be said of other rodent and primate models currently used in evaluating drugs for possible benefit in Parkinson's disease.

factors that contribute to the low predictive value include the high degree of species specificity in clinical responses to anti-parkinsonian agents, partly due to inter-species differences in brain bioavailability and dosing, and – as noted above – the lack of any relevant relationship of the acute MPTP lesion to the etiology and pathogenesis of cell death in PD. Positive results in the MPTP model do not assure positive results in the PD patients, and negative results in the MPTP mouse do not assure negative results in PD patients. There are many examples of agents that proved effective in the MPTP mouse, 6-OHDA rodent[5], or MPTP monkey, and later failed in PD patients. Indeed, in the history of modern Parkinson's disease therapy, far more of the agents that had first proved promising in these animal models subsequently failed in human clinical trials than ultimately warranted regulatory approval for use in human therapy.

22. We recently reported on one such failure. TCH346 (N-methyl-N-propargyl-10-aminomethyl-dibenzo[b,f]-oxepin) showed tremendous promise as an anti-Parkinsonian agent in preclinical studies. TCH346 had been shown to prevent degeneration of dopamine neurons in various *in vitro* models of programmed cell death, and also to protect against behavioral abnormalities and neurodegeneration in animal models of Parkinson's disease, including MPTP-treated monkeys. *See, e.g.*, Andringa *et al.*, "TCH346 prevents motor symptoms and loss of striatal FDOPA uptake in bilaterally MPTP-treated primates," *Neurobiol. Dis.* 14:205-217 (2003) (Exhibit 72). On the basis of impressive preclinical data, we conducted a large scale, international, multi-center, double-blind, placebo-controlled randomized controlled trial of TCH346 to establish whether TCH346 had similar effects in idiopathic Parkinson's disease, as measured by a delay in the emergence of disability sufficient to necessitate treatment with a dopaminergic drug. After 12 – 18 months' treatment, no significant differences were observed between any of the three TCH346 doses tested and placebo with respect to the primary or any of the secondary efficacy variables. In addition to the failure to show neuroprotection, there was no evidence of any symptomatic effect. *See* Olanow *et al.*, "TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial," *Lancet Neurol.* 5:1013-1020 (2006) (Exhibit 73) ("*Lancet Neurology* report").

[5] Unilateral lesion of the substantia nigra with 6-hydroxy-dopamine model is another well-known animal model.

23. Quoting from our *Lancet Neurology* report, "[t]he discrepancy between the preclinical promise of TCH346 and the clinical outcome could have arisen because of the use of laboratory models that do not accurately reflect the pathogenesis of Parkinson's disease, the doses of study drug used, insensitive clinical endpoints, and the patient population selected for study."

> There are several factors that could account for why TCH346 and other promising drugs, such as glial-cell-derived neurotrophic factor, work so well in laboratory models but are ineffective in patients with Parkinson's disease. Laboratory models used to test putative neuroprotective drugs, such as 6-hydroxydopamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), induce acute damage, which is restricted to dopamine neurons and thus might not accurately reflect the pathogenesis of cell death in Parkinson's disease. Thus, the neuroprotective effects observed in these models may be irrelevant to the human disease. The precise cause of Parkinson's disease in most cases is not known, making it difficult to precisely model the disease in the laboratory. Trangenic models. . . have not yet been able to reproduce the behavioural or pathological features of the disease. More recently, the sporadic form of the disease has been linked to defects in proteasomal function and systemic exposure of rats to proteasome inhibitors has been reported to induce a progressive levodopa-responsive model with behavioural, imaging, pathological, and biochemical features that closely replicate Parkinson's disease. However, there have been conflicting reports on the reproducibility of this model.

24. Other drugs that proved promising in MPTP models, and later failed in the clinic, include the A2A antagonist Istradephylline, the glutamate receptor antagonist talampemol, the anti-apoptotic agents CEP1347 and TCH346, direct infusion of the trophic factor GDNF, and transplantation of fetal nigral cells or retinal pigmented epithelial cells (spheramine), and gene delivery of the trophic factor Neurturin.

25. Turning to the Fredriksson reference, there are several specific aspects of the reported experiments that particularly reduce the predictive value of these experiments, and thus

warrant particular mention. To understand these problems, it is necessary to review the relevant experimental protocols and results.

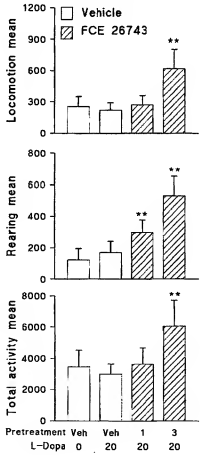
26. The Fredriksson authors report the results of two different experiments in MPTP-treated BL/6 mice, which they term an "acute" experiment with "subthreshold" levodopa and a "chronic" experiment with what they call "suprathreshold" levodopa. It is important to note that the terms "acute" and "chronic" do not refer to chronicity of safinamide treatment; in both cases, the mice were administered a single dose of safinamide. They refer only to whether the dose of levodopa was administered on a single or on multiple occasions.

27. In the "acute" experiment, C57 BL/6 mice were lesioned with MPTP four to six weeks prior to the experimental measurement. On the day of the experiment, safinamide was administered subcutaneously (s.c.) at 1, 3 or 10 mg/kg, followed one hour later with L-Dopa at 5 mg/kg. Activity and rearing levels were measured for the 2 hour period immediately thereafter. At the dosages used, "[n]either . . . FCE 26743 [safinamide] . . . nor L-Dopa (5 mg/kg) induced any behavioural effects by themselves." That is, the L-Dopa dose was, when given alone, a "subthreshold" dose and did not induce any beneficial effects. By contrast, "[t]he combination of FCE 26743, administered 60 min before, with L-Dopa produced, dose-differentially, a stimulation of motor activity in the MPTP-treated mice that were otherwise clearly hypokinetic."

28. In the "chronic" experiment, C57 BL/6 mice were first lesioned with MPTP. Animals were then treated with L-Dopa by administration of 20 mg/kg L-Dopa each weekday between weeks 3 and 8 for a total of 25 administrations. This treatment was intended to induce tolerance and to model the phenomenon known as "wearing off", in which the durability of the therapeutic benefit of L-Dopa in Parkinson disease patients is found to decrease (or wear off) over time. It should be noted that the MPTP rodent model is not a reliable model of "wearing off", nor is levodopa treatment administered once a day for 5 days a week for 5 weeks considered among practitioners and researchers in the PD community to be a model of tolerance. In the Fredriksson experiment, the "tolerized" mice were administered safinamide at 1, 3, or

10 mg/kg s.c. one hour prior to L-Dopa administration, as in the "acute" experiment. Fredriksson reports that administration of safinamide at 1 or 3 mg/kg one hour before a 20 mg/kg L-Dopa injection restored some L-Dopa activity in these "tolerized" mice.

29. Although Fredriksson labels the 20 mg/kg dose of L-Dopa in the "chronic" experiment as a "suprathreshold" dose, the terminology is misleading: as with the "subthreshold" 5 mg/kg dose in the "acute" experiment, the 20 mg/kg L-Dopa dose in the "chronic" experiment **is itself ineffective and does not reverse MPTP-caused motor deficits**; accordingly, the L-Dopa dose in the "chronic" experiment should more properly have been labeled as a "subclinical" dose. This can best be seen by comparing the two left-most bars in each histogram of Fredriksson's FIG. 6, reproduced below: in the absence of pretreatment with safinamide, the administration of 20 mg/kg L-Dopa has no significant effect on any of the measured activities:



30. At the time, safinamide was already known to have potent and selective MAO-B inhibitory activity,6 and would on that basis reasonably have been predicted to be effective as monotherapy in the treatment of Parkinson's disease (see my own reports on selegiline and lazabemide, *e.g.*, Parkinson's Study Group, Olanow CW, Steering Committee, "Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease," *N. Eng. J. Med.* 328:176-183 (1993) (Exhibit 75)). All Fredriksson adds to the then-existing body of knowledge is evidence that pretreatment with a single dose of safinamide can improve the efficacy of L-Dopa at doses of L-Dopa that, by themselves, are ineffective in what he terms the "acute" and "chronic" MPTP models. This result is not inconsistent with safinamide's known MAO-B inhibitory activity.

31. Limited to experimental conditions in which L-Dopa was administered at doses that by themselves were clinically ineffective, **the Fredriksson experiments simply do not model or mimic any phenomenon that is relevant to treatment of Parkinson's patients**: physicians would never administer subtherapeutic doses of L-Dopa. Indeed, subtherapeutic doses of levodopa might worsen the parkinsonian status of a PD patient by acting on presynaptic dopamine receptors and thereby inhibiting dopamine synthesis and release. **The Fredriksson data simply do not speak to the relevant question, whether concurrent administration of safinamide would increase the therapeutic efficacy of therapeutically-effective doses of L-Dopa**.

32. In addition, Fredriksson administered safinamide parenterally, by subcutaneous injection. Safinamide is being developed as an oral, not subcutaneous, treatment for Parkinson's disease. This is an important distinction. Effects seen with parenteral administration often will not reliably predict effects obtained oral administration, and *vice versa*. The reason is that drugs administered orally are subject to first-pass metabolism in the liver, whereas drugs administered parenterally are not. Orally administered agents can thus have a very different pharmacologic

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6 Strolin-Benedetti *et al.*, "The anticonvulsant FCE 26743 is a selective and short-acting MAO-B inhibitor devoid of inducing properties towards cytochrome P450-dependent testosterone hydroxylation in mice and rats," *J. Pharm. Pharmacol.*46:814-819 (1994) (Exhibit 74); U.S. Pat. No. 5,502,079 (of record).

profile (and are often effectively different drugs) than when the same agent is administered via the subcutaneous route.

33. This point is well illustrated by an example from my own lab.

34. By the mid-1990s, L-(-)-deprenyl (Selegiline) was used in clinical practice as an adjunct to levodopa therapy, having been shown to provide improved function and reduced motor fluctuations in patients with advanced disease. When Selegiline was first introduced into clinical practice, the therapeutic benefits were attributed to Selegiline's reasonably selective inhibition of MAO-B. However, work in my laboratory and various other laboratories suggested that Selegiline might also prevent neuronal degeneration through a mechanism independent of MAO-B activity. We demonstrated that much of the neuroprotective effect was properly attributable to the principal metabolite of selegiline, desmethylselegiline (DMS), which resulted from hepatic metabolism of the parent molecule. We showed that DMS protected dopamine neurons at significantly lower concentrations, and provided significantly greater levels of protection at the same concentrations, as the parent molecule, Selegiline. *See*, Mytilineou *et al.*, "L-(-)-desmethylselegiline, a metabolite of Selegiline [L-(-)-Deprenyl], protects mesencephalic dopamine neurons from excitotoxicity in vitro," *J. Neurochem.* 68:434-436 (1997) (Exhibit 76). Indeed inhibition of the CYP450 system, which blocked the metabolism of Selegiline and the formation of the DMS metabolite, blocked neuroprotection found with Selegiline. Based on our work, we believe that the DMS metabolite is responsible for the protective effects seen with Selegiline in the MPTP monkey. The neuroprotective effects of Selegiline simply would not have been predicted from data obtained using parenteral administration, which results in dramatically reduced concentrations of the DMS metabolite.

35. These observations also have important clinical implications. We were involved in the development of transdermal patch delivery of Selegiline, which allows Selegiline to bypasses liver metabolism. We found that patch delivery of Selegiline resulted in a 60-fold higher plasma concentration of the parent compound with a comparable reduction in its DMS metabolite in comparison to oral administration. As a consequence, patch Selegiline was able to

deliver much higher concentrations of the parent molecule to the brain, which resulted in an antidepressant effect (for which the drug is currently approved) that was not seen with comparable oral doses. In contrast, it would be anticipated that any protective effects of the drug observed with oral administration in PD, would not be seen with the transdermal delivery system. As the parent compound is thought to be responsible for the symptomatic effect and the metabolite for the protective effect, this example illustrates how oral and parenteral administration can lead to differing clinical effects. Indeed, patch Selegiline is currently approved for the treatment of depression in doses that were ineffective with oral Selegiline treatment.

36. Finally, adverse events that occur in rodent models do not necessarily occur in PD patients. Conversely, adverse effects may develop in the PD patients that were not seen in the mouse model; indeed, unanticipated adverse events are the commonest reason for a drug not making it to market. Some examples are mesulergine and other dopamine agonists (testicular adenomas in rats but not in PD patients), pramipexole and other dopamine agonists (retinal degeneration in albino mice and rats but not in PD patients), tolcapone (liver toxicity in PD patients but minimal evidence of this problem in rodents).

37. For all these reasons, it is my opinion that the animal model data in the Fredriksson reference would not have provided a person of ordinary skill in the art, in April 2003, with a reasonable expectation that the oral administration of safinamide would increase the therapeutic efficacy of ***clinically-relevant*** (that is, therapeutically effective) doses of L-Dopa being concurrently administered to patients with idiopathic Parkinson's disease.

D. Chazot and Fariello

38. The Chazot and Fariello references, alone or in combination with Fredriksson, do not change my opinion.

39. Chazot reviews the biochemical, pharmacological, and clinical properties of safinamide as had been reported publicly through early 2001. Several of these properties would readily have been understood to make safinamide an attractive candidate for continued development: potent use-dependent Na^+ channel- and also Ca^{++} channel-blocking activity, implying possible neuroprotective activity through inhibition of ion-driven glutamate release; good oral bioavailability; lack of toxicity in phase I human clinical trials. All of these would have been understood to encourage further development of safinamide for use in treating idiopathic Parkinson's disease. None of these properties, however, would have suggested that safinamide be developed for adjunctive use, *i.e.*, for use as an add-on to clinically-relevant doses of L-Dopa in patients with Parkinson's disease. Nor would any of the properties reported in Chazot, alone or in conjunction with the Fredriksson disclosure, have led to a reasonable expectation that oral administration of safinamide would increase the therapeutic efficacy of a clinically relevant dose of concurrently administered L-Dopa in the treatment of idiopathic Parkinson's disease.

40. The Fariello abstract discloses that PNU-151774E (safinamide) provides protective effects for dopamine neurons in the MPTP mouse model and increases rotations in the 6-OHDA rat model. As described above, numerous agents have failed in clinical trials of PD despite positive results in these models. Further, neither of these models suggests that addition of safinamide will enhance anti-parkinsonian responses in patients with idiopathic PD who are receiving effective doses of levodopa.

E. Concluding Remarks

41. At times in this Declaration, I have referred to a person of ordinary skill in the art of Parkinson's disease treatment. For clarity, I would say that this hypothetical person is a person with a PhD in neuroscience or pharmacology, or a person with an MD and special training in neurology.

42. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements and the like so made may jeopardize the validity or enforceability of U.S. Patent Application Serial No. 10/559,982, or any patent that issues therefrom.

6/20/09
Date

C. Warren Olanow, M.D.